British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) **82** 1303–1307 1303

REVIEW

CYP2C19 and CYP2D6 genotypes in Pacific peoples

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Received 23 May 2016; **Revised** 10 June 2016; **Accepted** 14 June 2016

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Keywords CYP2C19, CYP2D6, Ethnicity, Pharmacogenetics

The study of pharmacogenetic variants in populations which reside in Oceania has been focused mainly on *CYP2C19* and *CYP2D6*. Statements about the high prevalence of *CYP2C19* no function genotype in 'Pacific Islanders' can be found in the literature. This review article summarizes the published information about these pharmacogenes in this geographical region and highlights the differences observed between Melanesian and Polynesian populations. It is not appropriate to combine the prevalence data of pharmacogenetic variants, particularly *CYP2C19*, across this region. Indeed, apocryphal assumptions about *CYP2C19* no function alleles and possible effect on the therapeutic activity of clopidogrel are unhelpful and reiterate the importance of assessing the individual patient rather than relying on inappropriate ethnicity-based assumptions for drug dosing decisions.

Introduction

The Western Pacific region broadly encompasses countries of Southeast Asia, such as the east coast of mainland China, Korea, Taiwan and Japan as well as the islands of Oceania. This latter region includes the large islands of Papua New Guinea, Australia and New Zealand as well as a myriad of smaller Pacific islands. There are more than 25 000 Pacific islands but many of these are uninhabited. The Pacific islands are divided into the regions of Micronesia (including Palau, Marianas, Caroline and Marshall Islands and Kiribati); Melanesia, an area extending from Papua New Guinea, via an archipelago of islands to New Caledonia and Fiji; and a vast area called Polynesia which extends from Hawai'i, Rapanui to the most southerly island in the Polynesian group, Aotearoa (New Zealand).

What is the difference between the Pacific peoples of Melanesia and Polynesia?

There is evidence that there have been multiple waves of migration of mankind into the Western Pacific region. Archaeological evidence suggests that humans crossed land bridges and arrived in Melanesia more than 45 000 years ago. Whole genome sequencing also suggests that anatomically modern humans may have coexisted and possibly admixed with Denisovan-like archaic hominids in this region [1]. At the end of the last ice age (<10 000 years ago) the populations of Papua New Guinea, Melanesia and Aboriginal Australians became geographically isolated from the later wave of migration of anatomically modern man into Southeast Asia and Indonesia. This links with the genomic ancestry cline observed between Melanesia and island Southeast Asia [2], which broadly corresponds to the biogeographic faunal discontinuity known as the Wallace line. A much later (~3000 years ago) wave of migration by sea, possibly from a region close to modern day Taiwan, is thought to have led to colonization of some of island Melanesia as well as the further expansion into the remote Polynesian islands such as Hawai'i, Rapanui and Aotearoa (New Zealand). Oral genealogical information indicates that the arrival of Maori in New Zealand occurred about 1000–800 years ago and more than forty separate waka (double hulled canoes) undertook this long journey. Many of the iwi (tribes) of Maori can trace their origins to the captains and crew of these waka.

DOI:10.1111/bcp.13045

Much of this human history of the Pacific can be ascertained from archaeological and linguistic studies. However, use of genome-wide single nucleotide polymorphism (SNP) data have also inferred these demographic relationships [3]. Hence, there are not only geographical but also substantial cultural and ethnic differences across this region, particularly between the populations residing in Melanesia and Polynesia. The complexities of ancestral demographics and geographic isolation, admixture with European settlers, as well as the possible confounding effects of natural disasters, especially on the small volcanic islands and atolls of the Pacific, can result in substantial bottleneck effects and may underpin the differences in the prevalence of genetic polymorphisms in drug-metabolizing enzymes between individual populations across Oceania.

CYP2C19

Oceania is considered to have the highest frequency of no function *CYP2C19* individuals of any geographical region. Consequently up to 58% of individuals from this region are expected to have a no function CYP2C19 'poor metabolizer' phenotype [4]. However, it is important to note that these values are determined from ethnically diverse populations from geographically distant regions (Table 1). These high prevalence values are particularly influenced by the data reported from more than 6978 individuals located in Melanesia, i.e. Papua New Guinea and Vanuatu [5–10] and also Australian aboriginal people [11]. Based on the data from Vanuatu, it was predicted 'that the poor metabolizer genotype is common throughout Polynesia and Micronesia' [7]. However, CYP2C19 status has only been assessed in 246 Polynesian individuals (3.4% of all Oceanian subjects tested) and there are no reports in Micronesian individuals. Moreover, many of these reports in Polynesian subjects have limitations, such as assessment of *CYP2C19* in cohorts of patients, e.g. Lupus nephritis and cardiovascular disease [12, 13], or have only assessed phenotype [14, 15]. Even with these limitations, the average prevalence of inherited *CYP2C19* poor metabolizer status in Polynesia is 8% and is substantially lower than the mean reported across Melanesia (50.1%; Table 1). In addition, the *CYP2C19*3* allele appears to be relatively uncommon in Polynesians compared with Melanesians, with an allele frequency of 0.04 *vs.* 0.19 (Table 1). The *CYP2C19*4* no function allele has not been assessed in Pacific peoples. The prevalence of the increased function allele *CYP2C19*17* is unclear (range 0.0–0.11) as two publications have assessed this variant and both these are from small subgroup observations in patient cohorts [12, 13].

Table 1

Prevalence of *CYP2C19* no function alleles reported in different populations and geographical regions across Oceania

Geographical region/Ethnicity	*CYP2C19*2*	*CYP2C19*3*	Homozygous no function *CYP2C19* (poor metaboliser)[a]	Number of subjects	Reference
Papua New Guinea (>6 individual locations)	0.45	0.16	36%	401	[9]
	0.37	0.34	49%	47[b]	[5]
	0.45	0.19	40%	172	[10]
Vanuatu (>24 individual locations)	0.71	0.13	70.8%	493	[6]
	0.63	0.14	61%	5538	[7]
	0.57	0.25	68%	100	[8]
Aboriginal Australians (1 location)	0.36	0.14	25.6%	227	[11]
Summary[c] of Melanesia	**0.51**	**0.19**	**50.1%**	**6978**	
Samoan, Tongan, Cook Islander, Niuean[d]	n.d.	n.d.	13%[e]	59	[15]
Samoan, Tongan, Fijian, Cook Islander[d,f]	0.14	0.07	4%	14	[12]
Maori and 'Pacific islanders'[d,g]	0.29	n.d.	8%	70	[13]
Maori	n.d.	n.d.	7%[d]	43	[14]
Maori	0.24	0.017	8%	60	[22]
Summary[c] of Polynesia	**0.22**	**0.04**	**8%**	**246**	

n.d., not determined
[a]Includes compound heterozygotes (*2/*3)
[b]Two locations excluded due to very small sample size
[c]Summary are mean values
[d]Self-identified ethnicity, resident in NZ
[e]Phenotyped only, no genotype information collected
[f]Lupus nephritis
[g]Cardiovascular disease

CYP2C19 and clinical outcomes in Pacific peoples

CYP2C19 poor metabolizers may have a poor therapeutic response to the chemoprophylactic antimalarial prodrug proguanil. Asymptomatic malaria-infected Vanuatuan children (Melanesia), who were *CYP2C19* homozygous for no function alleles, had a significantly lower formation of cycloguanil, the active metabolite of proguanil, than individuals who were not carriers of no function alleles. Indeed many of these poor metabolizer individuals had no detectable cycloguanil formation [8]. However, the response of *Plasmodium vivax* or *Plasmodium falciparum* infection to treatment with proguanil did not correlate with no *CYP2C19* genotype [16]. It is possible that adequate blood concentrations of proguanil were achieved in these *CYP2C19* no function children who had mild or asymptomatic infection as the parent compound has some intrinsic (albeit weak) antimalarial activity. Thus, the high prevalence of this genetic polymorphism in this geographic location may have no clinical consequence in this particular context.

The presence of no function *CYP2C19*2* is strongly associated with an increased risk of a stent thrombosis when on clopidogrel therapy [17]. Maori and Pacific Island patients do appear to have a significantly higher rate of 'high on clopidogrel platelet reactivity' compared to New Zealand Europeans (57% *vs*. 35.9%, [18]). However, this study did not assess *CYP2C19* genotype. In a separate study [19], although not directly measured, a higher prevalence of *CYP2C19*2* allele frequency was assumed in Maori (0.24) and Pacific islanders (0.45) compared to European New Zealanders (0.15). Based on these prevalence values, no *CYP2C19*2* gene dose association was observed for rates of stent thrombosis across these ethnicities (event rates: 0.3%, 0.3% and 0.2% for European, Maori and Pacific Islanders, respectively), or for other events, such as bleeding, myocardial infarction, stoke or cardiovascular death. Direct assessment of *CYP2C19* genotype was undertaken in a more recent study of 312 New Zealand patients, of whom 70 were Maori and Pacific islanders [13]. The *CYP2C19*2* allele could only explain 3–4% of the variability of on-treatment platelet reactivity and this study reiterated the known importance of clinical variables such as comorbidities and co-medications in clopidogrel outcomes, which accounted for 18% of this variability. There is a high rate of type 2 diabetes in Maori and Pacific Islanders in New Zealand with rates reported to be 218–370 per 100 000 compared to 97 per 100 000 in the total New Zealand population (http://www.stats.govt.nz/). Poor cardiovascular outcomes are a known consequence of chronic diabetes and Maori and Pacific islanders have a higher rate of myocardial infarction and cardiovascular death on clopidogrel treatment than European patients [19]. Importantly, regardless of ethnicity, only diabetes and *CYP2C19*2* were independent contributors to poor control of platelet reactivity on clopidogrel treatment in this New Zealand cohort [13].

In 2014 the Attorney General of the state of Hawai'i raised concerns that certain pharmaceutical suppliers of clopidogrel had failed 'to disclose that a significant proportion of patients in Hawai'i had genetic polymorphism in the [*CYP2C19* gene]' [20]. It is important to note that the assumption that the prevalence of CYP2C19 poor metabolism is high in Polynesians is not supported by the current literature, and the direct assessment of this genotype in Hawai'ian Polynesians has not been reported. Despite this lack of evidence, articles raise the concern that 'the standard 75 mg dose of clopidogrel is not efficacious for Hawaiians' [21]. These authors also state 'As a total population some 150,000–300,000 Hawaiians will have a reduced enzymatic capacity to convert clopidogrel to its active metabolite'. Such apocryphal statements are clearly unhelpful, particularly as data from a New Zealand cohort of Polynesians support the known importance of clinical comorbidities in clopidogrel treatment outcomes for patients with acute coronary syndromes.

CYP2D6 in Pacific peoples

The CYP2D6 poor metabolizer phenotype has been reported at 5% frequency in Maori, using debrisoquine as a probe drug [14]. *CYP2D6* allelic variants that either lack enzyme activity (**4,*5*) or result in decreased activity (**41*) appear to be present at relatively low frequency in Maori compared to Caucasian Europeans [22]. An absence of the CYP2D6 poor metabolizer phenotype has been reported in 'South Pacific Polynesians' [15] and a low frequency of CYP2D6 poor metabolizer status (1%) is also predicted from the assessment of *CYP2D6*4*, **10 and *41* alleles in subjects from Papua New Guinea [10] and is based on genotype data. The poor metabolizer phenotype is also predicted to be relatively low in (0.4%) in Australian Aboriginal people [11]. Furthermore, *CYP2D6* genotype data of a small cohort of patients in Auckland suggests that the prevalence of no/decreased function *CYP2D6* alleles may be lower in Maori and Pacific islanders than in New Zealand Europeans [23]. These limited data suggest that *CYP2D6* no function genotype is not common in Polynesian or Melanesian individuals (as reviewed in [24]). However, a proportion of individuals in some of these studies [10, 23] could not be assigned a genotype (no call) suggesting additional unidentified sequence variations or novel haplotype(s) of known SNPs within these populations. *CYP2D6* gene duplication (*CYP2D6*2*xN) , associated with an ultrarapid metabolizer phenotype, was observed at 0.12 frequency in subjects from Papua New Guinea [10]. This duplication, however, was absent in Australian aborigines [11] and little is known about the prevalence of this gene duplication in Polynesians and other Pacific Islanders. There do not appear to have been any clinical studies to assess different clinical outcomes in Pacific peoples based on *CYP2D6* genotype.

The prevalence of some other CYP enzymes, such as *CYP2C9* and *CYP2A6* have been reported in Maori [22], *CYP2E1* in Aboriginal Australians [11] and *CYP2B6* in Papua New Guinea [25]; however, it is not possible to compare these prevalence rates across the geographic locations and ethnicities of the Pacific.

Conclusions

The prevalence of *CYP2D6* no function phenotype is likely to be low in populations of Polynesian and Melanesian ancestry,

although this is based on limited evidence. In contrast, substantial data indicate that *CYP2C19* no function variants are very common in Melanesians, but these variants appear to be much less frequent in the small number of Polynesian individuals tested. Based on the demographics of human history in the Pacific region, it is clear that substantial differences exist between people of Melanesian and Polynesian ancestry. It is not appropriate to combine the prevalence data of pharmacogenetic variants, particularly *CYP2C19*, across this vast region. Statements about the high prevalence of *CYP2C19* no function genotype in 'Pacific Islanders' are apocryphal and unhelpful. Assumptions about the presence of no activity pharmacogenetic variants based on apparent and/or self-reported ethnicity is never appropriate. Dosing decisions, when justified for the safe and effective use of a particular medication, should be based on the known genotype of the individual patient.

Competing Interests

There are no competing interests to declare.

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